Asian Journal of Advanced Research and Reports

11(3): 37-47, 2020; Article no.AJARR.58489
ISSN: 2582-3248

Role of Vitamin E in Prevention of Breast Cancer: An Epidemiological Review

Md. Sajjadul Haque Ripon[1], Mohammad Asadul Habib[1*], Miraz Hossain[1], Nadim Ahmed[1], Tanbir Kibria[1], Shirajum Munira[2] and Kamrul Hasan[1]

[1]Department of Food Technology and Nutrition Science, Noakhali Science and Technology University, Sonapur-3814, Bangladesh.
[2]Department of Food and Nutrition, College of Home Economics, University of Dhaka, Bangladesh.

Authors' contributions

This work was carried out in collaboration among all authors. Author MSHR carried out the studies, participated in the sequence alignment, performed in the analysis of the findings and drafted the manuscript. Authors MAH and MH in the design of the study, sequence alignment and amp; drafted the manuscript. Authors NA, TK, KH and SM conceived of the study and participated in its design and helped to draft the manuscript. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/AJARR/2020/v11i330266
Editor(s):
(1) Dr. Maria Luisa Kennedy Rolon, Universidad Nacional de Asunción, Paraguay.
Reviewers:
(1) Monica, Manipal Academy of Higher Education, Dubai.
(2) Abdul Karim Suhag, Sindh Madressatul Islam University, Pakistan.
Complete Peer review History: http://www.sdiarticle4.com/review-history/58489

Review Article

Received 19 April 2020
Accepted 24 June 2020
Published 01 July 2020

ABSTRACT

Breast cancer rates are so high among women in more developed countries, rates are increasing in almost every region of the world. In 2018, it is reported that 627,000 women died from breast cancer. Vitamin E is a common supplement characterized by its antioxidant potential effects on many chronic conditions that prevent free radicals from harming DNA, protein and cell membranes may serve as a part of cancer growth by reducing oxidative DNA alteration. The major forms of vitamin E as an anticancer agent, which acts as major antioxidants to regulate peroxidation reactions and control free-radical production within the body, are tocopherols and tocotrienols. Since Vitamin E had first acted as a non-antioxidant, α-tocopherol has inhibited smooth muscle proliferation activity and protein kinase C activity. Although tocotrienols are mostly investigated as antioxidant effects of tocotrienol, which plays an important role in reducing the damage to DNA by decreasing the by-product of lipid peroxidation. This study aims to investigate the connection between vitamin E and also the risk of breast cancer and the outcome is that some inverse

**Corresponding author: Email: asadulhabib698@gmail.com;*

relationship between vitamin E and breast cancer exists. There has been clear evidence that vitamin E reduces the risk of human cancer but our main focus is on breast cancer, seen in many prospective and retrospective case-control, cohort and intervention studies.

Keywords: Vitamin E; cancer; tocopherols; tocotrienols; epidemiologic studies.

ABBREVIATIONS

OFR : Oxygen free radicals
RONS : Reactive oxygen and nitrogen species
α-T : α-Tocopherol
δ-T : δ-Tocotrienol
α-TTP : α-Tocopherol transfer protein
TAP : Tocopherol-associated protein
TBP : Tocopherol-binding protein
TRF : Tocotrienol-rich fraction
Pre-M : Pre-menstrual
Post-M : Post- menstrual

1. INTRODUCTION

Countries in South Asia face a secret epidemic of breast cancer [1]. Breast cancer is the most frequent cancer among women, impacting 2.1 million women each year, and also causes considerable number of cancer-related deaths among women. In 2018, it is reported that 627,000 women died from breast cancer – this is approximately 15 % of all cancer deaths among women. While breast cancer rates are so high among women in more developed countries, rates are increasing in almost every part of the world [2]. While breast cancer is primarily a postmenopausal women's disease in developed countries (less than 50years), almost half of all cases of breast cancer (45%) in developing countries were diagnosed in 2010 in reproductive women (15-49 years) [3]. We estimate that 30,000 women in cases of breast cancer will have an annual new burden in Bangladesh. In South Asia, the incidence of breast cancer in combination with increased life expectancy and population growth [4] and the adoption of "Western" lifestyles (higher fat diets, less activity, reduction in parity, delayed childbirth, and decreased breastfeeding) is expected to increase [5]. While countries with high incomes are celebrating dramatic advances in breast cancer care for women, countries with low incomes, such as Bangladesh, are just beginning to realize how severe and dangerous the disease is [4–6].

The leading cause of death within the world is currently breast cancer, which is the leading malignancy (neoplasm tumor) diagnosed in women, which is about 25% of all cancers, that of 15% of all deaths of cancer [7-8]. More than half of the women who have been diagnosed with breast cancer in the world do not seem to be due to known disease risk factors [9]. The risk of cancer by free radicals acting on biological systems through oxidative processes is increased by these poisonous chemicals [10].

Natural antioxidants are neutralized in free radicals, which cause tissue damage to molecules with one or more unpaired electrons [11]. Free radicals are produced through ionizing radiation in normal or pathological cell metabolism. An important characteristic of radicals and free radicals' reaction is their lead to new radicals, leading to chain reactions [12]. Despite antioxidant defense like vitamin E, damage to proteins and DNA associated with OFR accumulates through life and is claimed to lead to breast cancer [13-15]. There has been compelling evidence over the last few years that the rise of the incidence of cancer in an aging population can be reversed through the removal of preventable OFR sources or improved antioxidant defense systems [16–18]. Diet and nutrition have been seen as a successful preventive method for cancer. Substantial experimental findings suggest that several natural dietary products could affect breast cancer growth and development, such as soy, pomegranate, mangosteen, citrus fruits, apple, grape, mango, cruciferous vegetables, ginger, garlic, black cumin, edible macro-fungi, and cereals [19]. Some recommended foods, such as probiotic products and lemon have patented the benefits of anticancer. Other major illnesses such as cardiovascular disease, hypertension, hypercholesterolemia, cancer, and other possible diseases can be suppressed and treated with probiotics [20]. Accumulated evidence from studies indicates that the dietary consumption of lemon and lemon products (such as lemon peel, lemongrass oil, lemon extract) supposes to be inversely correlated with the decreased risk of various infectious diseases and cancers [21].

Of all the foundations of cancer treatment, chemotherapy is one. While the procedure increases cancer patients' survival, it causes

substantial toxicity. In addition to acute toxicity such as nausea, alopecia, oral mucositis, and depression in the bone marrow, long-term side effects are going to reduce these patients' standard of life. The cross-linking of radical-mediated DNA is one of the ways in which most treatment medicines have their cytotoxic effects [22,23].

The body has several ways to combat oxidative stress by generating antioxidants, which are produced either naturally or given externally by food (exogenous). The antioxidants' role is to neutralize the excess of free radicals, protect cells from their toxic effects, and reduce oxidative DNA alteration to prevent tissue, organ damage, and primary cancer prevention [24]. Our dietary antioxidants play a key role in the neutralization of oxidative stress by endogenous antioxidants. The structure and antioxidant function of each of the nutrients is unique [25]. They will also interfere with the action of therapeutic agents acting alone through the production and induction of apoptosis by reactive oxygen species [26]. The proposal has been made to protect the breast tissues from oxidizing damage that might lead to the development of cancer by lipid-based soluble antioxidants, such as vitamin E [27]. Lipid-soluble antioxidants, such as vitamin E, have been suggested to protect the breast tissue from oxidant damage that can lead to cancer development [28]. The current evidence for a relationship between vitamin E as antioxidant and breast cancer will be examined in this review. This paper aims to examine the relation between vitamin E and the risk of breast cancer as well.

2. EXECUTIVE SUMMARY

The health benefits of vitamin E, including antioxidants, neuroprotective and anti-increasing properties, are well-known. A vital, fat-soluble nutrient that works as an antioxidant within the human body was found in vitamin E [29]. Tocopherol is derived mainly from vegetable oils and animal fats, which are of critical importance in body membranes and represent a group of compounds divided by two sub-groups called tocopherols and tocotrienols. They serve as important antioxidants that control peroxidation and free radical production within the body [30,31]. The eight different forms of this family of compounds are in the two categories: 4 saturated analogs (α, β, γ, and δ), known as tocopherols, and 4 unsaturated analogs known as tocotrienols [29-31].

2.1 Tocopherols as Anticancer Agents

A category of phenolic fat-soluble compounds is the tocopherols, the principal form of vitamin E (Fig. 1). Each tocopherol consists of a chromanol ring and a sixteen carbon phytyl chain. Tocopherols are called α, β, γ and δ depending on the quantity and location of the methyl teams on the chromanol ring. Alpha-tocopherol (α-T) is tri-methylated at the ring's 5-7-and-8- specific locations, and β-T is di-methylate at 5-and 8-specific locations, whereas γ-T is di-methylate at 7-, 8- specific locations and δ-T is methylated at 8-specific locations [33]. The 5- and 7-position non-methylated carbons are electrophilic centers, capable of effectively trapping reactive oxygen and nitrogen (RONS). All tocopherols are strong antioxidants but α-T and α-T are more effective than α-T at trapping reactive nitrogen species and effectively mitigates lipid-free radicals by reducing single-electron. This is potentially the most important physiological antioxidant mechanism to secure biological membranes [33, 34]. Vegetable oils, such as corn oils, soybeans, sesame, and nuts are the major dietary sources of tocopherols. In these oils, γ-T is 3 to 5 times higher than α-T, and δ-T is as abundant as α-T, whereas β-T exists in only minimum amounts [35, 36]. However, γ-T rich mixture of tocopherols (γ-TmT) is a by-product in the distillation of vegetable oil and usually contains (per gram) 130 mg α-T, 15 mg β-T, 568 mg γ-T, and 243 mg δ-T has demonstrated for cancer prevention activities [37-39].

As a result of vitamin E's first non-antioxidant function, α-tocopherol inhibited smooth muscle growth and protein kinase c. Since then, three proteins have been specifically identified for binding tocopherols: α-tocopherol transfer protein (α-TTP), tocopherol-associated protein (TAP), and tocopherol-binding protein (TBP).α-TTP is a 30–35 k Di protein (a baculoviral protein that prevents apoptosis in virus-infected cells) located in the liver moving α-tocopherol preferentially from the liver to the blood [40-42]. Thus α-tocopherol is the major tocopherol found in human blood and tissues [43]. Tocopherols are known to inhibit lipid oxidation from hydroxyl radicals as well as alkoxyl radicals, peroxyl radicals, singlet oxygen, and possibly the number of oxygen and metal complexes. These agents do not alone harm lipids. However, produce secondary intermediates, lipid hydroperoxides that start a chain reaction of lipid peroxidation, and decompose into alcohol and organic peroxyl radicals. Tocopherols protect lipids without

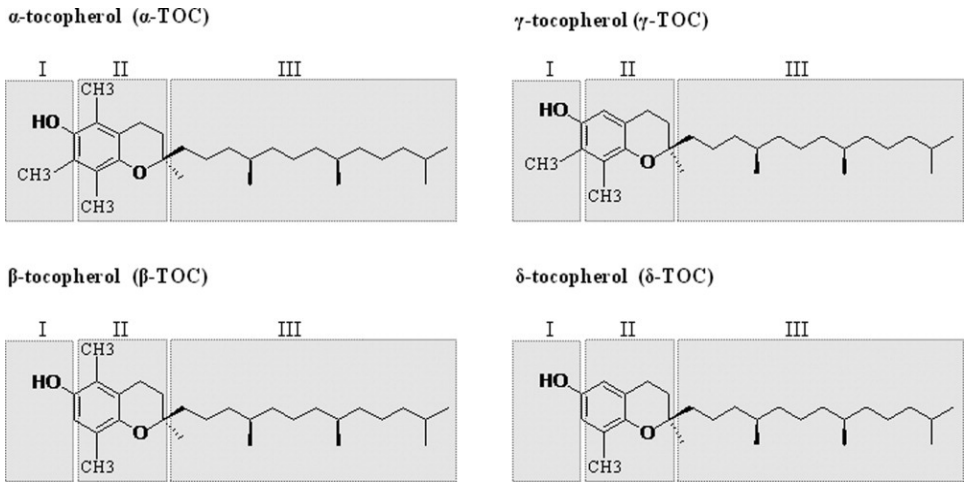

Fig. 1. Chemical structures of α-, β-, γ-, and δ-tocopherols [32]

reacting in further chain propagation steps through scavenging peroxyl radicals [44-46].

Many studies indicate that a lower nutritional status of vitamin E is associated with a greater risk of certain cancers so that it is proposed that tocopherols reduce cancer risk [47, 48]. α-T has therefore been the most commonly used form of tocopherols, which are more capable of acting as a prooxidant for cancer prevention studies than γ-tocopherol and δ-tocopherol. However, the findings of large-scale human intervention experiments using α-T such as the Alpha-Tocopherol-Beta-Carotene Cancer Prevention Experiment and the Selenium-Vitamin E Cancer Prevention Studies have led to conflicting conclusions on the cancer prevention activities of tocopherols [49].

2.2 Tocotrienols as Anticancer Agents

Tocotrienols contain a phenolic hydroxyl group on the number of 6 carbon of the chromanol ring as well as tocopherols. Classified as α, β, γ, and δ which act as the reactive site responsible for mediating antioxidant activities, depending on the number and the position of methyl groups within the chromanol ring. While tocotrienols are also potent antioxidants that interfere with peroxidation and control the body's free-radical generation (Fig. 2) [33, 34]. Breast cancer is primarily screened for cancer to determine tocotrienol anti-cancer activity [50, 51]. In one trial tocotrienols showed significant in vitro anticancer activity in the normal mammalian epithelial cells against extremely malignant mammalian Cancer cells with minimum toxicity [52]. The anti-cancer activity was measured by decreased proliferation. Furthermore, the reduced activity of Akt (protein kinase B) and of NF-kB (a protein complex that controls transcription of DNA, cytokine production, and cell survival) was shown to mediate tocotrienol reduced mammalian cancer cell proliferation [53]. A recent animal study showed significant reductions in oxidant DNA damage from the consumption of tocotrienol. Oxidative stress-induced DNA damage is the primary cause of the genetic mutation in mammalian cells. The damage to unrepaired DNA builds up and may result in cancer. Tocotrienol has recently been suggested to play a protective function from oxidative stress DNA damage that could contribute to its chemo-preventive function [54]. Tocotrienol seems to have a major anti-oxidant effect since the decreased damage to DNA was associated with a decrease in lipid peroxidation by-products [55]. Initially, studies investigating the effects of high dietary intakes of fat on mammary tumorigenesis in a laboratory found that the use of fatty diets significantly stimulates the development of carcinogenic mammary tumors [56, 57]. Other research studies have investigated the effects of dietary vitamin E supplementation from palm oil, commonly known as the tocotrienol-rich fraction (TRF) mixture, containing α-tocopherol (20%), α- tocotrienol (16%), γ-tocotrienol (44%), δ-tocotrienol (15%) and non-vitamin E contaminants (5%). That supplementation inhibited mammal's tumor cell proliferation and induced cell death in a dose-responsive manner [50,52,58]. Direct comparisons among the two subclasses in

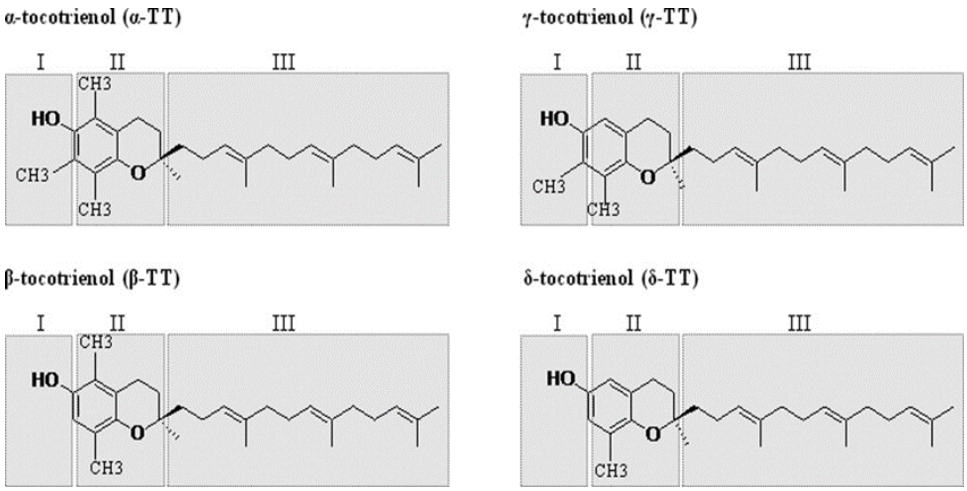

Fig. 2. Chemical structures of α-, β-, γ- and δ-tocotrienols [32]

Table 1. Case-control studies of vitamin e and breast cancer risk

Population location and study year	Case/Control number	Intake or blood levels of vitamin E (case vs. controls)	The inverse relationship between vitamin E level and cancer risk	Reference
India (2002)	54/42 (Total Population) Pre-M: 28/23 Post-M:26/19	Serum α-T: (25 vs. 28) μmol/L Serum α-T: (25 vs. 38) μmol/L Serum α-T: (25 vs. 30) μmol/L	Yes	60
Malaysia (2008)	57/139	Vitamin E: (6.1 vs. 6.9) mg/day	Yes	61
Italy (1991-1994)	2569/2588	Blood vitamin E level is not specified.	Yes	62
US (2010)	297/311	Blood vitamin E level is not specified.	Yes	63
South Korea (2004-2006)	362/362	(10.6 vs. 11.2) Mg/day	No	64

vitamin E have shown that tocotrienols are much more powerful than tocopherols for suppressing growth and inducing cell death [52,59]. Such research studies also indicate that tumor cells are substantially more sensitive than normal mammalian epithelial cells to the anti-proliferative and apoptotic behavior of tocotrienols [52,59]. These studies were generally the experimental evidence of tocotrienols' anti-cancer activity and suggested that such vitamin E may be potentially used for the treatment of breast cancer in women as a chemotherapeutic agent [50,52,58,59].

3. RESULTS

In most cases, samples and active trials concentrate on breast cancer, and human cancer research is performed. Such studies have been performed in women with vitamin E, especially in premenstrual and postmenstrual women. These hypotheses showed that there was a significant difference between α-T plasma levels and higher dietary intake of rich vitamin E food over a long time between the subsequent cancer-causing group and the non-cancer-causing group (Table 1) [60-64].

Different experimental designs in retrospective and prospective case-control have commonly been used to test a hypothesis that the plasma level of α-T is inversely associated with the risk of cancer. The studies were listed in Table 2. Most future research, however, use people in both men and women who do not eat additional

Table 2. Human epidemiologic studies on the relationship between vitamin e level and cancer risk

Type of case-control study	Sample size	Case and control number	Intake or serum vitamin E level of case and controls	Case and controls difference	The inverse relationship between vitamin E level and cancer risk	References
Prospective	5,004 women	39\78	(4.6vs 6) mg\dl	1.4 mg\dl	Yes	65
Prospective	15,093 women	313\578	(10 vs. 10.38) mg\L	0.38 mg\L	Yes	66
Prospective	295 men and women	99\196	(10.5 vs.11.9) mg\L	1.4 mg\L	Yes	67
Prospective	36,265 men and women	150\276	Men-(7.83vs 8) mg\L women-(9.87 vs. 10.7) mg\L	M-0.17 mg\L W-0.83 mg\L	Yes	68
Prospective	5086 women	30\288	(6.5 vs. 6.2) mg\L	(-0.03) mg\L	No	69
Prospective	321 men and women	111\210	(1.16 vs. 1.26) mg\dl	0.1 mg\dl	No	70
Retrospective	260 women	108\152	(0.97 vs. 0.96) mg\dl	(-0.01) mg\dl	No	71

vitamin E. Diets and lifestyles differ considerably between individuals in these populations; this may lead to major changes in plasma vitamin E levels. In fact, in both cases and controls, marking fluctuations in vitamin E plasma levels have been observed. Such problems led to inconsistent results on the relationship between plasma vitamin E and the risk of cancer in human epidemiological studies [65-71].

4. DISCUSSION

Many control studies using vitamin E, four studies showed a reduction of risk of breast cancer, but one did not find a combination of the incidence of breast cancer (Table 1). In breast cancer patients, vitamin E was measured at the different clinical stage and menopausal status of 54 patients with breast cancer, 28 were premenopausal, and 26 were post-menopausal. The levels of Plasma Vitamin E had a certain association, with low levels associated with much greater cancer risk. The disparity in the mean amounts of vitamin E between the cases and controls was 3 µmol / L; and 13 µmol / L and 5 µmol / L respectively for the pre- and postmenopausal women. The total nutrient consumption of vitamin E and plasma vitamin E was in contrast to controls substantially lower in cases [60]. Differential serum vitamin E levels and higher dietary vitamin E diet rich in cases and control studies in pre-post menstrual women have been observed in these studies. The inverse association between vitamin E and breast cancer has been shown to be a major difference in serum vitamin E levels and the consumption of vitamin E rich food in cases or controls. There were considerable differences in the serum vitamin E levels in these four studies between the cases and controls. Women with the lowest α-T quintile were more likely to develop cancer [60-63]. However, one study did not establish an association with the incidence of breast cancer because it is difficult to show a reverse relationship between vitamin E and cancer, because of the lack of significant differences in vitamin E levels between case and control [64].

In humans, numerous experimental retrospective and prospective case-control designs were performed to establish the association of vitamin E with cancer (Table 2). Numerous case-control studies utilized vitamin E and four studies found a risk reduction (65–68), but three studies found no association with the incidence of breast cancer [69–71]. The plasma levels of α-T of 39 women who eventually developed breast cancer

were assessed in a prospective study of 5,004 participants, and of 78 controls who did not. The plasma levels of vitamin E showed a certain correlation, with low levels correlated with much higher cancer risk. In cases and controls the mean vitamin E levels were 4.7mg\L and 6.0mg\L. Cancer incidence was approximately five times higher for the lowest quintile's women with vitamin E compared to the highest quintile's women with vitamin E [65]. Similarly, serum α-T was measured for a similar study of 15,093 women who participated in the Finnish Social Insurance Institution's Mobile Clinic Health Survey. Among this survey study, 313 women were developed cancer and 578 controls that did not. There has been an inverse association between serum vitamin E concentration and cancer risk. Women with the lowest α-T quintile were 1.6 times more likely to have cancer than women with the highest α-T quintiles. In all cancer cases, the average amount of serum α-T was around 10 mg\L and 10.38 mg\L in the controls (66). Another prospective study with 295 men and women measuring serum vitamin E levels from 99 cases to 196 controls where vitamin E was lower in the cases than the controls (10.5±3.2 vs. 11.9±4.90 mg per liter). Due to large standard deviations, the vitamin E values between cases and controls have to overlap considerably. The risk of lung cancer was 2.5 times greater for those with the lowest quintile vitamin E levels than for those who had the highest quintile vitamin E levels [67]. Serum vitamins E and Se in 150 individuals who have developed gastrointestinal cancer and 276 controls that did not have been determined in a prospective study of 36,265 Finnish men and women. For both men and women, the mean value of α-T for cases was 7.83 mg\L and 9.87 mg\L where 8 mg\L and 10.7 mg\L were respectively for controls. The risk of cancer of the upper gastrointestinal tract was increased for subjects with low concentrations of α-T [68].

However, in the same prospective study, 5,086 people were screened between 30 cases and 288 controls for serum vitamin E. The α-T value was 6.5 mg\L and 6.2 mg\L respectively, for both cases and controls. The inverse association of serum vitamin E levels to the risk of breast cancer was not observed [69]. Another prospective study involving 321 men and women were measured with serum vitamin E levels within 111 cases and 210 controls. Serum vitamin E levels were somewhat lower in subjects who later had cancer than in controls and vitamin E levels for case and controls were 1.16 mg\dl and 1.26 mg\dl respectively where the case-control difference was 0.1 mg\dl. These findings do not support the hypothesis about antioxidant vitamin E intake or serum levels at a reduced cancer risk (70). The dietary supplement and the plasma α- T levels were assessed with α-T values for the cases of women 0.97 mg\dl and for the controls 0.969 mg\dl respectively in a retrospective case-control analysis involving 108 cancer cases and 152 controls. Measuring the plasma or serum levels at just one or two times and without any great vitamin E differences between cases and controls makes it extremely difficult to establish a definite possible connection between the plasma vitamin E level and the risks of cancer. The plasma vitamin E levels and the risk of cancer were also not inversely related. However, as discussed earlier, this retrospective experimental design is not appropriate for such a conclusion [71].

5. CONCLUSION

This review summarizes the studies based on epidemiology, interventions and experiments related to cancer prevention activities of tocopherols and tocotrienols as an anticancer agent of vitamin E. In addition, the antioxidant and anticancer activities of the individual members of various subgroups of Vitamin E are of a wide variety. In particular, tocotrienols are significantly more anti-proliferative and apoptotic than tocopherols in a number of experimental models of breast cancer, indicating that dietary supplementation tocotrienols can avoid or decrease the risk of breast cancer in women. The relationship between single vitamins and the risk of breast cancer was the most significant. However, further research appears to be justified on whether vitamin E plays a role in the prevention of breast cancer. Vitamin E serum levels are likely preferable to dietary recall because they reflect long-term exposure. Tissue oxidant damage measurements and α-tocopherol levels could be even more informative as this site reflects the intake and use of action. A pilot study is being undertaken to determine if α-tocopherol and oxidative damage in the breast tissue levels can be measured and utilized as risk markers for breast cancer. In summary, breast cancer is a serious universe problem, and progress in preventing breast cancer would be very useful in significantly reducing the burden of breast cancer risk and death among women. Dietary antioxidant supplementation, particularly vitamin E, is associated with cellular dysfunction and death to protect against free-radical damage.

Although dietary changes are not easy in an attractive breast cancer prevention procedure. As the animal evidence is promising, there have been limited but promising evidence from human studies, and vitamin E is so safe, additional vitamin E and breast cancer risk associations are predicted.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Hossain MS, Ferdous S, Karim-Kos HE. Breast cancer in South Asia: A Bangladeshi perspective. Cancer epidemiology. 2014;38 (5):465-70.
2. WHO. Cancer: Breast cancer. (Accessed: 22 june 2020) Available:https://www.who.int/cancer/prevention/diagnosis-screening/breast-cancer/en/
3. Forouzanfar MH, Foreman KJ, Delossantos AM, Lozano R, Lopez AD, Murray CJ, et al. Breast and cervical cancer in 187 countries between 1980 and 2010: A systematic analysis. The lancet. 2011;378(9801):1461-84.
4. Wilson C, Tobin S, Young R. The exploding worldwide cancer burden. International Journal of Gynecologic Cancer. 2004;14 (1):1-11.
5. Porter P. Westernizing" women's risks? Breast cancer in lower-income countries. New England Journal of Medicine. 2008; 358(3):213.
6. Story H, Love R, Salim R, Roberto A, Krieger J, Ginsburg O. Improving outcomes from breast cancer in a low-income country: lessons from Bangladesh. International Journal of Breast Cancer; 2012.
7. Ben-Chioma AE, Obunwo CC, Ebirien – Agana BS, Ndokiari B. Some heavy metal assay in urine of breast cancer and breast cancer free patients in Port Harcourt, Nigeria. European Journal of Pharmaceutical and Medical Research. 2017;4 (12):91–95.
8. Traber MG, Packer L. Vitamin E: beyond antioxidant function. The American journal of clinical nutrition. 1995;62(6):1501S-9S.
9. Ben-Chioma A, Obunwo C, Ebirien–Agana B, Ndokiari B. Evaluation of heavy metal levels in the serum of breast cancer patients in Port Harcourt, Nigeria. International Journal of Contemporary Medical Research. 2018;4(12):1-5.
10. Bhattacharya A, Seshadri M, Oven SD, Tóth K, Vaughan MM, Rustum YM. Tumor vascular maturation and improved drug delivery induced by methylselenocysteine leads to therapeutic synergy with anticancer drugs. Clinical Cancer Research. 2008;14 (12):3926-32.
11. Freeman BA, Crapo JD. Biology of disease: free radicals and tissue injury. Laboratory investigation; A Journal of Technical Methods and Pathology. 1982;47(5):412-26.
12. Halliwell B, Gutteridge J. Oxygen toxicity, oxygen radicals, transition metals and disease. Biochemical Journal. 1984;219 (1):1.
13. Dreher D, Junod AF. Role of oxygen free radicals in cancer development. European Journal of cancer. 1996;32(1):30-8.
14. Halliwell B, Gutteridge JM, Cross CE. Free radicals, antioxidants, and human disease: where are we now? The Journal of laboratory and clinical medicine. 1992;119 (6):598-620.
15. Ames BN, Shigenaga MK, Hagen TM. Oxidants, antioxidants, and the degenerative diseases of aging. Proceedings of the National Academy of Sciences. 1993;90(17):7915-22.
16. Guyton K, Kensler TW. Oxidative mechanisms in carcinogenesis. British Medical Bulletin. 1993;49(3):523-44.
17. Feig DI, Reid TM, Loeb LA. Reactive oxygen species in tumorigenesis. Cancer Research. 1994;54(7 Supplement):1890s-4s.
18. Cerutti PA. Oxy-radicals and cancer. Lancet (British edition). 1994;344(8926):862-3.
19. Li Y, Li S, Meng X, Gan RY, Zhang JJ, Li HB. Dietary natural products for prevention and treatment of breast cancer. Nutrients. 2017;9(7):728.
20. Habib MA, Mamun MAA, Kabir MR, Chowdhury MH, Tumpa FA, Nayeem J. Probiotics for cardiovascular diseases, hypertension, hypercholesterolemia and cancer condition: A summary of the evidence. Education Quarterly Reviews. 2019;2(2).
21. Habib MA, Kawsar Hossen M, Amin A. Anti-Carcinogenic Effect of Lemon &

Lemon Products in Cancer Therapy: A Summary of the Evidence; 2019.
22. Raber-Durlacher J, Weijl N, Saris MA, De Koning B, Zwinderman A, Osanto S. Oral mucositis in patients treated with chemotherapy for solid tumors: a retrospective analysis of 150 cases. Supportive Care in Cancer. 2000;8(5):366-71.
23. Hartley JA, Reszka K, Lown JW. Photosensitization by antitumor agents, 4. Anthrapyrazole-photosensitized formation of single strand-breaks in DNA. Free Radical Biology and Medicine. 1988;4(6): 337-43.
24. Pham-Huy LA, He H, Pham-Huy C. Free radicals, antioxidants in disease and health. International Journal of Biomedical Science: IJBS. 2008;4(2):89.
25. Rao PS, Kalva S, Yerramilli A, Mamidi S. Free radicals and tissue damage: Role of antioxidants. Free Radicals and Antioxidants. 2011;1(4):2-7.
26. Ratnam DV, Ankola D, Bhardwaj V, Sahana DK, Kumar MR. Role of antioxidants in prophylaxis and therapy: A pharmaceutical perspective. Journal of Controlled Release. 2006;113(3):189-207.
27. Baum M. Prospects for the chemoprevention of breast cancer. Control of Growth Factors and Prevention of Cancer: Springer. 1992;67-74.
28. London R, Murphy L, Kitlowski KE. Breast cancer prevention by supplemental vitamin E. Journal of the American College of Nutrition. 1985;4(5):559-64.
29. Nesaretnam K. Multitargeted therapy of cancer by tocotrienols. Cancer Letters. 2008;269(2):388-95.
30. Palozza P, Simone R, Picci N, Buzzoni L, Ciliberti N, Natangelo A, et al. RETRACTED: Design, synthesis, and antioxidant potency of novel α-tocopherol analogues in isolated membranes and intact cells. Elsevier; 2008.
31. Palozza P, Verdecchia S, Avanzi L, Vertuani S, Serini S, Iannone A, et al. Comparative antioxidant activity of tocotrienols and the novel chromanyl-polyisoprenyl molecule FeAox-6 in isolated membranes and intact cells. Molecular and cellular biochemistry. 2006;287(1-2):21-32.
32. Constantinou C, Papas A, Constantinou AI. Vitamin E and cancer: An insight into the anticancer activities of vitamin E isomers and analogs. International Journal of Cancer. 2008;123(4):739-52.
33. Traber M, Bowman B, Russell R. Present knowledge in nutrition. Washington, DC: ILSI Press; 2006.
34. Ju J, Picinich SC, Yang Z, Zhao Y, Suh N, Kong AN, et al. Cancer-preventive activities of tocopherols and tocotrienols. Carcinogenesis. 2010;31(4):533-42.
35. Eitenmiller RR, Lee J. Vitamin E: food chemistry, composition and analysis: CRC Press; 2004.
36. Qian J, Morley S, Wilson K, Nava P, Atkinson J, Manor D. Intracellular trafficking of vitamin E in hepatocytes: The role of tocopherol transfer protein. Journal of lipid research. 2005;46(10):2072-82.
37. Lu G, Xiao H, Li GX, Picinich SC, Chen YK, Liu A, et al. A γ-tocopherol-rich mixture of tocopherols inhibits chemically induced lung tumorigenesis in A/J mice and xenograft tumor growth. Carcinogenesis. 2010;31(4):687-94.
38. Huang Y, Khor TO, Shu L, Saw CLL, Wu TY, Suh N, et al. A γ-tocopherol-rich mixture of tocopherols maintains Nrf2 expression in prostate tumors of TRAMP mice via epigenetic inhibition of CpG methylation. The Journal of Nutrition. 2012;142(5):818-23.
39. Barve A, Khor TO, Nair S, Reuhl K, Suh N, Reddy B, et al. γ-Tocopherol-enriched mixed tocopherol diet inhibits prostate carcinogenesis in TRAMP mice. International Journal of Cancer. 2009;124 (7):1693-9.
40. Boscoboinik D, Szewczyk A, Azzi A. α-Tocopherol (vitamin E) regulates vascular smooth muscle cell proliferation and protein kinase C activity. Archives of Biochemistry and Biophysics. 1991;286(1):264-9.
41. Boscoboinik D, Szewczyk A, Hensey C, Azzi A. Inhibition of cell proliferation by alpha-tocopherol. Role of protein kinase C. Journal of Biological Chemistry. 1991;266 (10):6188-94.
42. Murphy DJ, Mavis R. Membrane transfer of. cap alpha.-tocopherol: Influence of soluble. cap alpha.-tocopherol-binding factors from the liver, lung, heart and brain of the rat. J Biol Chem; (United States). 1981;256(20).
43. Brigelius-Flohe R, Traber MG. Vitamin E: function and metabolism. The FASEB Journal. 1999;13(10):1145-55.
44. Cadenas E, Ginsberg M, Rabe U, Sies H. Evaluation of α-tocopherol antioxidant activity in microsomal lipid peroxidation as

detected by low-level chemiluminescence. Biochemical Journal. 1984;223(3):755-9.
45. Reed DJ, Fariss MW, Pascoe GA. Mechanisms of chemical toxicity and cellular protection systems. Toxicological Sciences. 1986;6(4):591-7.
46. Pascoe GA, Reed DJ. Vitamin E protection against chemical-induced cell injury: II. Evidence for a threshold effect of cellular α-tocopherol in prevention of adriamycin toxicity. Archives of Biochemistry and Biophysics. 1987;256(1):159-66.
47. Taylor PR, Qiao Y-L, Abnet CC, Dawsey SM, Yang CS, Gunter EW, et al. Prospective study of serum vitamin E levels and esophageal and gastric cancers. Journal of the National Cancer Institute. 2003;95(18):1414-6.
48. Mahabir S, Schendel K, Dong YQ, Barrera SL, Spitz MR, Forman MR. Dietary α-, β-, γ-and δ-tocopherols in lung cancer risk. International Journal of Cancer. 2008;123 (5):1173-80.
49. Lippman SM, Klein EA, Goodman PJ, Lucia MS, Thompson IM, Ford LG, et al. Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). Jama. 2009;301(1):39-51.
50. Nesaretnam K, Stephen R, Dils R, Darbre P. Tocotrienols inhibit the growth of human breast cancer cells irrespective of estrogen receptor status. Lipids. 1998;33(5):461.
51. Sylvester PW, Akl MR, Malaviya A, Parajuli P, Ananthula S, Tiwari RV, et al. Potential role of tocotrienols in the treatment and prevention of breast cancer. Biofactors. 2014;40(1):49-58.
52. McIntyre BS, Briski KP, Gapor A, Sylvester PW. Antiproliferative and apoptotic effects of tocopherols and tocotrienols on preneoplastic and neoplastic mouse mammary epithelial cells (44544). Proceedings of the Society for Experimental Biology and Medicine. 2000;224(4):292-301.
53. Shah SJ, Sylvester PW. Tocotrienol-induced cytotoxicity is unrelated to mitochondrial stress apoptotic signaling in neoplastic mammary epithelial cells. Biochemistry and Cell Biology. 2005;83 (1):86-95.
54. Budin SB, Othman F, Louis SR, Bakar MA, Das S, Mohamed J. The effects of palm oil tocotrienol-rich fraction supplementation on biochemical parameters, oxidative stress and the vascular wall of streptozotocin-induced diabetic rats. Clinics. 2009;64(3): 235-44.
55. Taridi N, Yahaya MF, Teoh SL, Latiff A, Ngah W, Das S, et al. Tocotrienol rich fraction (TRF) supplementation protects against oxidative DNA damage and improves cognitive functions in Wistar rats. La Clinica Terapeutica. 2011;162(2):93-8.
56. Sylvester PW, Ip C, Ip MM. Effects of high dietary fat on the growth and development of ovarian-independent carcinogen-induced mammary tumors in rats. Cancer Research. 1986;46(2):763-9.
57. Sylvester PW, Russell M, Ip MM, Ip C. Comparative effects of different animal and vegetable fats fed before and during carcinogen administration on mammary tumorigenesis, sexual maturation and endocrine function in rats. Cancer Research. 1986;46(2):757-62.
58. Yu W, Simmons-Menchaca M, Gapor A, Sanders BG, Kline K. Induction of apoptosis in human breast cancer cells by tocopherols and tocotrienols; 1999.
59. Sylvester P, McIntyre B, Gapor A, Briski K. Vitamin E inhibition of normal mammary epithelial cell growth is associated with a reduction in protein kinase Cα activation. Cell proliferation. 2001;34(6):347-57.
60. Ray G, Husain SA. Role of lipids, lipoproteins and vitamins in women with breast cancer. Clinical Biochemistry. 2001; 34(1):71-6.
61. Suzana S, Normah H, Fatimah A, Fadilah RN, Rohi GA, Amin I, et al. Antioxidant intake and status and oxidative stress in relation to breast cancer risk: A case-control study. Asian Pacific J Cancer Prev. 2008;9 (2):343-50.
62. Negri E, La Vecchia C, Franceschi S, D'Avanzo B, Talamini R, Parpinel M, et al. Intake of selected micronutrients and the risk of breast cancer. International Journal of Cancer. 1996;65(2):140-4.
63. Freudenheim JL, Marshall JR, Vena JE, Laughlin R, Brasure JR, Swanson MK, et al. Premenopausal breast cancer risk and intake of vegetables, fruits and related nutrients. JNCI: Journal of the National Cancer Institute. 1996;88(6):340-8.
64. Yang YJ, Hwang SH, Kim HJ, Nam S-J, Kong G, Kim MK. Dietary intake of nitrate relative to antioxidant vitamin in relation to breast cancer risk: A case-control study. Nutrition and Cancer. 2010;62(5):555-66.

65. Wald N, Boreham J, Hayward J, Bulbrook R. Plasma retinol, β-carotene and vitamin E levels in relation to the future risk of breast cancer. British Journal of Cancer. 1984;49 (3):321-4.
66. Knekt P. Serum vitamin E level and risk of female cancers. International Journal of Epidemiology. 1988;17(2):281-6.
67. Menkes MS, Comstock GW, Vuilleumier JP, Helsing KJ, Rider AA, Brookmeyer R. Serum beta-carotene, vitamins A and E, selenium, and the risk of lung cancer. New England Journal of Medicine. 1986;315(20): 1250-4.
68. Knekt P, Aromaa A, Maatela J, Alfthan G, Aaran RK, Teppo L, et al. Serum vitamin E, serum selenium and the risk of gastrointestinal cancer. International Journal of Cancer. 1988;42(6):846-50.
69. Russell M, Thomas B, Bulbrook R. A prospective study of the relationship between serum vitamins A and E and risk of breast cancer. British Journal of Cancer. 1988;57(2):213-5.
70. Willett WC, Polk BF, Underwood BA, Stampfer MJ, Pressel S, Rosner B, et al. Relation of serum vitamins A and E and carotenoids to the risk of cancer. New England Journal of Medicine. 1984;310 (7): 430-4.
71. Stryker WS, Stampfer MJ, Stein EA, Kaplan L, Louis TA, Sober A, et al. Diet, plasma levels of beta-carotene and alpha-tocopherol, and risk of malignant melanoma. American Journal of Epidemiology. 1990;131(4):597-611.

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